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Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

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1. EXECUTIVE SUMMARY

Ethylene oxide (EtO) is a gas at room temperature. It is manufactured from ethylene and used primarily as a chemical intermediate in the manufacture of ethylene glycol. It is also used as a sterilizing agent for medical equipment and a fumigating agent for spices.

CHARACTERIZATION OF THE CARCINOGENIC HAZARD

The DNA-damaging properties of EtO have been studied since the 1940s. EtO is known to be mutagenic in a large number of living organisms, ranging from bacteriophage to mammals, and to induce chromosome damage. It is carcinogenic in mice and rats, inducing tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland. In humans employed in EtO-manufacturing facilities and in sterilizing facilities, there is strong evidence of an increased risk of cancer of the lymphohematopoietic system and of breast cancer in females. Increases in the risk of lymphohematopoietic cancer have been seen in most (but not all) of the epidemiological studies of EtO-exposed workers, manifested as an increase either in leukemia or in cancer of the lymphoid tissue. Of note, one large epidemiologic study conducted by the National Institute for Occupational Safety and Health (NIOSH) of sterilizer workers that had a well-defined exposure assessment for individuals reported positive exposure-response trends for lymphohematopoietic cancer mortality, primarily in males and in particular for lymphoid cancer (i.e., non-Hodgkin lymphoma [NHL], myeloma, and lymphocytic leukemia), and for breast cancer mortality in females (Steenland et al., 2004). The positive exposure-response trend for female breast cancer was confirmed in an incidence study based on the same worker cohort (Steenland et al., 2003). There is supporting evidence for an association between EtO and breast cancer from other studies, but the database is more limited than that for lymphohematopoietic cancers, in part because there are not as many studies that include sufficient numbers of females.

Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, EtO is characterized as "carcinogenic to humans" by the inhalation route of exposure based on the total weight of evidence, in accordance with the U.S. Environmental Protection Agency's (EPA's) 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). The lines of evidence supporting this characterization include: (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans

and progress to tumors, including evidence of chromosome damage in humans exposed to EtO. Overall, confidence in the hazard characterization of EtO as "carcinogenic to humans" is high.

DERIVATION OF THE INHALATION UNIT RISK ESTIMATE

Inhalation unit risk estimates were developed for evaluating the potential cancer risks posed by inhalation exposure to EtO. The unit risk estimates for cancer mortality and incidence were based on the human data from the NIOSH study (Steenland et al., 2004; Steenland et al., 2003). This study was selected for the derivation of risk estimates because it is a high-quality study,[1] it is the largest of the available studies, and it has exposure estimates for the individual workers from a high-quality exposure assessment. Multiple modeling approaches were evaluated for the exposure-response data, including modeling the cancer response as a function of either categorical exposures or continuous individual exposure levels. Model selection for each cancer data set was primarily based on a preference for models of the individual-level continuous exposure data, prioritization of models that are more tuned to local behavior in the low-exposure data, and a weighing of statistical and biological considerations.

Unit risk estimates based on the human data were first derived under the common assumption that relative risk is independent of age. This assumption is later superseded by an assumption of increased early-life susceptibility, and it is the unit risk estimates derived under this latter assumption that are the ultimate estimates proposed in this assessment (presented further below).

Under the assumption that relative risk is independent of age, an LEC_{01} (lower 95% confidence limit on the EC_{01}, the estimated effective concentration associated with 1% extra risk) for excess lymphoid cancer mortality (Steenland et al., 2004) was calculated using a life-table analysis and the lower spline segment from a two-piece linear spline model. Linear low-dose extrapolation below the range of observations is supported by the conclusion that a mutagenic mode of action is operative in EtO carcinogenicity. Linear low-dose extrapolation from the LEC_{01} for lymphoid cancer mortality yielded a lifetime extra cancer unit risk estimate of 1.1×10^{-3} per $\mu g/m^3$ (2.0×10^{-3} per ppb)[2] of continuous EtO exposure. Applying the same lower-spline regression coefficient and life-table analysis to background lymphoid cancer *incidence* rates and applying linear low-dose extrapolation resulted in a preferred lifetime extra lymphoid cancer unit risk estimate of 2.9×10^{-3} per $\mu g/m^3$ (5.3×10^{-3} per ppb), as cancer incidence estimates are generally preferred over mortality estimates.

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[1]The NIOSH study (Steenland et al., 2004; Steenland et al., 2003) was judged to be a "high-quality" study based on the attributes discussed in Section 3.1 and in Section A.2.8 of Appendix A, including availability of individual worker exposure estimates from a high-quality exposure assessment, cohort study design, large size, inclusion of males and females, adequate follow-up, absence of any known confounding exposures, and use of internal comparisons. The breast cancer incidence study using the subcohort of female workers with interviews had the additional attribute of investigating and controlling for a number of breast cancer risk factors (Steenland et al., 2003).

[2]Conversion equation: 1 ppm = 1,830 $\mu g/m^3$.

Breast cancer incidence risk estimates were calculated directly from the data from a breast cancer incidence study of the same occupational cohort (Steenland et al., 2003). Using the same life-table approach, the lower spline segment from a two-piece linear spline model, and linear low-dose extrapolation, a unit risk estimate of 8.1×10^{-4} per $\mu g/m^3$ (1.5×10^{-3} per ppb) was obtained for breast cancer incidence. A unit risk estimate for breast cancer mortality was also calculated from the cohort mortality data; however, the incidence estimate is preferred over the mortality estimate.

Combining the incidence risk estimates for the two cancer types resulted in a total cancer unit risk estimate of 3.3×10^{-3} per $\mu g/m^3$ (6.1×10^{-3} per ppb).[3]

Unit risk estimates (for total cancer) were also derived from the three chronic rodent bioassays for EtO reported in the literature. These estimates, ranging from 2.2×10^{-5} per $\mu g/m^3$ to 4.6×10^{-5} per $\mu g/m^3$, are about two orders of magnitude lower than the estimate based on human data. The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis than rodent data for estimating population risks (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided. Although there is a sizeable difference between the rodent-based and the human-based estimates, the human data are from a large, high-quality study, with EtO exposure estimates for the individual workers and little reported exposure to chemicals other than EtO. Therefore, the estimates based on the human data are the preferred estimates for this assessment.

Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and as there are no chemical-specific data from which to assess early-life susceptibility, increased early-life susceptibility should be assumed, according to the EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*—hereinafter referred to as the "EPA's *Supplemental Guidance*" (U.S. EPA, 2005b). This mode-of-action-based assumption of increased early-life susceptibility supersedes the assumption of age independence under which the human data-based estimates presented above were derived. Thus, using the same approach and exposure-response models as for the estimates discussed above but initiating exposure in the life-table analysis at age 16 instead of at birth, adult-exposure-only unit risk estimates were calculated for lymphoid cancer incidence and breast cancer incidence under an alternate assumption that relative risk is independent of age for adults, which represent the life stage pertaining to the occupational cohort data which were used for the exposure-response modeling. These adult-exposure-only unit risk estimates were then rescaled to a 70-year basis for use in the standard age-dependent adjustment factors (ADAFs) calculations and risk estimate calculations involving less-than-lifetime exposure scenarios. The resulting adult-based unit risk estimates were 2.6×10^{-3} per $\mu g/m^3$ (4.8×10^{-3} per ppb) for lymphoid

[3]The method used to derive the total cancer unit risk estimate involves estimating an upper bound on the sum of the maximum likelihood estimates of risk; see Section 4.1.3.

cancer incidence, 7.0×10^{-4} per $\mu g/m^3$ (1.3×10^{-3} per ppb) for breast cancer incidence in females, and 3.0×10^{-3} per $\mu g/m^3$ (5.5×10^{-3} per ppb) for both cancer types combined. The adult-based unit risk estimates, which were derived under an assumption of increased early-life susceptibility, supersede those presented earlier that were derived under the assumption that relative risk is independent of age. When using the adult-based unit risk estimates to estimate extra cancer risks for a given exposure scenario, the standard ADAFs should be applied, in accordance with the EPA's *Supplemental Guidance* (U.S. EPA, 2005b). Applying the ADAFs to obtain a full lifetime total cancer unit risk estimate yields 5.0×10^{-3} per $\mu g/m^3$ (9.1×10^{-3} per ppb), and the commensurate lifetime chronic (lower-bound) exposure level of EtO corresponding to an increased cancer risk of 10^{-6} is 2×10^{-4} $\mu g/m^3$ (1×10^{-4} ppb).

The unit risk estimate is intended to provide a reasonable upper bound on cancer risk from inhalation exposure. The estimate was developed for environmental exposure levels (it is considered valid for exposures up to about 40 $\mu g/m^3$ [20 ppb]) and is not applicable to higher level exposures, such as those that may occur occupationally, which appear to have a different exposure-response relationship (see below for a summary of risk estimates for occupational exposure scenarios).

CONFIDENCE IN THE UNIT RISK ESTIMATE

The primary sources of uncertainty in the unit risk estimates derived from the human data include the retrospective exposure assessment conducted for the epidemiology study, the exposure-response modeling of the epidemiological data, and the low-dose extrapolation.[4] Despite uncertainties in the unit risk estimate, confidence in the estimate is relatively high. First, confidence in the hazard characterization of EtO as "carcinogenic to humans," which is based on strong epidemiological evidence supplemented by other lines of evidence, is high. Second, the unit risk estimate is based on human data from a large, high-quality epidemiology study with individual worker exposure estimates. Retrospective exposure estimation is an inevitable source of uncertainty in this type of epidemiology study; however, the NIOSH investigators put extensive effort into addressing this issue by developing a state-of-the-art regression model to estimate unknown historical exposure levels using variables, such as sterilizer size, for which historical data were available. In addition, the two-piece spline models used in this assessment to model the supralinear exposure-response relationships are considered to provide a reasonable basis for the derivation of unit risk estimates. Finally, the use of linear low-exposure extrapolation is strongly supported by the conclusion that EtO carcinogenicity has a mutagenic mode of action.

Confidence in the unit risk estimate is particularly high for the breast cancer component, which is based on over 200 incident cases for which the investigators also had information on other potential breast cancer risk factors. The selected model for the breast cancer incidence data provided a good

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[4]See Section 4.1.4 for additional discussion of these and other sources of uncertainty in the unit risk estimates.

global fit as well as a good local fit in the lower exposure range of greatest relevance for the derivation of a unit risk estimate. The actual unit risk might be higher or lower; however, considering the continuous-exposure linear model as a lower bound for the supralinear exposure-response relationship suggests that while a unit risk estimate for breast cancer incidence that is up to fourfold lower is plausible, unit risk estimates lower than that are considered unlikely from the available data. Sensitivity analyses for lag time, inclusion of covariates, knot, upper-bound estimation approach, use of the full incidence cohort, and inclusion of only invasive cancers for the breast cancer background rates in the life table indicate that the unit risk estimate is not highly influenced by these factors, with comparison unit risk estimates differing by at most 40%.

There is somewhat less, although still relatively high in general, confidence in the lymphoid cancer component of the unit risk estimate because it is based on fewer events (53 lymphoid cancer deaths); incidence risk was estimated from mortality data; and the exposure-response relationship is exceedingly supralinear, complicating the exposure-response modeling and model selection to a greater extent than for breast cancer incidence. The actual unit risk might be higher or lower than that from the selected model, and there were no clear upper or lower bounds for the apparent exposure-response relationship provided by other models. Sensitivity analyses for lag time, knot, and upper-bound estimation approach, indicate that the unit risk estimate for lymphoid cancer is more influenced by these factors than was the estimate for breast cancer incidence. Comparison unit risk estimates from the sensitivity analyses ranged from about 50% of the preferred unit risk estimate to about three times that estimate. While there is less confidence in the lymphoid cancer unit risk estimate than in the breast cancer unit risk estimate, the lymphoid cancer estimate is considered a reasonable estimate from the available data, and overall, there is relatively high confidence in the total cancer unit risk estimate.

RISK ESTIMATES FOR OCCUPATIONAL EXPOSURE SCENARIOS

As noted above, the inhalation unit risk estimate was developed for environmental exposure levels (up to about 40 $\mu g/m^3$ [20 ppb]) and is not applicable to higher exposure levels, such as those that may occur occupationally, which appear to have a different exposure-response relationship. However, occupational exposure levels of EtO are of concern to the EPA when EtO is used as a pesticide (e.g., sterilizing agent or fumigant). Therefore, this document also presents estimates of extra risk for the two cancer types for a range of occupational inhalation exposure scenarios (see Section 4.7). Maximum likelihood estimates of the extra (incidence) risk of lymphoid cancer and breast cancer combined for the range of occupational exposure scenarios considered (i.e., 0.1 to 1 ppm 8-hour time-weighted average [TWA] for 35 years) ranged from 0.037 to 0.11; upper-bound estimates ranged from 0.081 to 0.22. The uncertainty associated with the extra risk estimates for occupational exposure scenarios is less than that associated with the unit risk estimates for environmental exposures, and the overall confidence in the extra risk estimates for occupational exposure is high. The extra risk estimates

are derived for occupational exposure scenarios that yield cumulative exposures well within the range of the exposures in the NIOSH study. Moreover, the NIOSH study is a study of sterilizer workers who used EtO for the sterilization of medical supplies or spices (Steenland et al., 1991); thus, the results are directly applicable to workers in these occupations, and these are among the occupations of primary concern to the EPA.

SUMMARY OF ASSESSMENT FINDINGS

Table 1-1 provides a summary of the major findings in this assessment.

Table 1–1. Summary of major findings

Hazard conclusions	
Hazard characterization	The weight of evidence from epidemiological studies and supporting information is sufficient to conclude that ethylene oxide is carcinogenic to humans.
Mode of action	The weight of evidence is sufficient to conclude that ethylene oxide carcinogenicity has a mutagenic mode of action.
Inhalation unit risk estimates (for environmental exposures)[a]	
Basis	**Inhalation unit risk estimate[a] (per µg/m³)[b]**
Full lifetime unit risk estimate (includes ADAFs)[c]	
Total cancer risk based on human data[d]—lymphoid cancer incidence and breast cancer incidence in females	**5.0×10^{-3}**
Adult-based unit risk estimates (for use with ADAFs)[e]	
Total cancer risk based on human data[d]—lymphoid cancer incidence and breast cancer incidence in females	**3.0×10^{-3}**
Lymphoid cancer incidence in both sexes based on human data	2.6×10^{-3}
Breast cancer incidence in females based on human data	7.0×10^{-4}
Total cancer incidence risk estimate from rodent data (female mouse)	4.6×10^{-5}
Extra risk estimates for occupational inhalation exposure scenarios (see Section 4.7)	
Maximum likelihood estimates of the extra risk of lymphoid cancer and breast cancer combined for the range of occupational exposure scenarios considered (i.e., 0.1 to 1 ppm 8-hr TWA for 35 yr)[f]	0.037–0.11
Upper-bound estimates of the extra risk of lymphoid cancer and breast cancer combined for the range of occupational exposure scenarios considered (i.e., 0.1 to 1 ppm 8-hr TWA for 35 yr)[f]	**0.081–0.22**

[a]These unit risk estimates are not intended for use with continuous lifetime exposure levels above about 40 µg/m³. See Section 4.7 for risk estimates based on occupational exposure scenarios. Preferred estimates are in bold.
[b]To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 (µg/m³)/ppm. Also, 1 ppb = 1.83 µg/m³.
[c]Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and because of the lack of chemical-specific data, the EPA assumes increased early-life susceptibility and recommends the application of ADAFs, in accordance with the EPA's *Supplemental Guidance* (U.S. EPA, 2005b), for exposure scenarios that include early-life exposures. For the full lifetime (upper-bound) unit risk estimate presented here, ADAFs have been applied, as described in Section 4.4.
[d]To be precise, this unit risk estimate reflects the total (upper-bound) cancer risk to females and not to the general population because the breast cancer risk estimate only applies to females. As a practical matter for regulatory purposes, however, females comprise roughly half the general population and this unit risk estimate enables risk managers to evaluate the individual risk for this substantial population group. For the purposes of estimating numbers of cancer cases attributable to specific exposure levels (e.g., for benefits analyses), it would be more appropriate to use the cancer-specific unit risk estimates (or central tendency estimates), taking sex into account.
[e]These (upper-bound) unit risk estimates are intended for use in ADAF calculations and less-than-lifetime adult exposure scenarios (U.S. EPA, 2005b). Note that these are not the same as the unit risk estimates derived directly from the human data in Section 4.1 under the assumption that RRs are independent of age. See Section 4.4 for the derivation of the adult-based unit risk estimates.
[f]Technically, these sums would reflect the total cancer risk to females and not a mixed-sex workforce because the breast cancer risk estimate only applies to females. As a practical matter for regulatory purposes, however, females typically comprise a substantial proportion of the sterilizer workforce and summing these extra risk estimates enables risk managers to evaluate the individual risk for this substantial workforce group. In a situation in which the workforce of concern is comprised predominantly of males, it might be appropriate to use a sex-weighted sum of the extra risks from the two cancer types (see Section 4.7 for the cancer-specific extra risk estimates).
hr = hour; yr = year.